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I, VIVIEN IRENE COULSON, declare:

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 96 Langley Road, Watford, Hertfordshire, WD17 4PJ;
2. That I am well acquainted with the French and English languages;
3. That the attached is a true translation into the English language of the certified copy of European Patent Application No. 03291601.7 filed 30 June 2003
4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

Declared this

19th

day of

September 2005

V.I. Coulson

V.I. COULSON



European
Patent Office

Certificate

The attached documents are exact
copies of the European patent
application described on the following
page, as originally filed.

Patent application No.

03291601.7

For the President of the
European Patent Office

[signature]

R C van Dijk



European
Patent Office

Application no.: 03291601.7

Date of filing: 30.06.03

Applicant(s):

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FRANCE

Title of the invention:
(If no title is shown please refer to the description.)

New process for the synthesis of perindopril and its pharmaceutically acceptable salts

Priority(ies) claimed
State/Date/File no.:

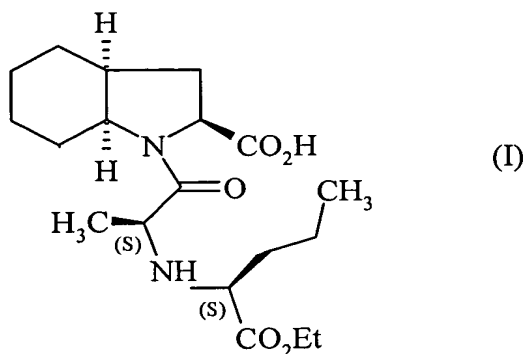
International Patent classification:

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Contracting states designated at date of filing:

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SE SI SK TR LI

The present invention relates to a process for the industrial synthesis of perindopril of formula (I) :



and its pharmaceutically acceptable salts.

- 5 Perindopril and its pharmaceutically acceptable salts, and more especially its tert-butylamine salt, have valuable pharmacological properties.

Their principal property is that of inhibiting angiotensin I converting enzyme (or kininase II), which allows, on the one hand, prevention of the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II (a vasoconstrictor) and, on the other hand, prevention of the degradation of bradykinin (a vasodilator) to an inactive peptide.

Those two actions contribute to the beneficial effects of perindopril in cardiovascular diseases, more especially in arterial hypertension and heart failure.

- 15 Perindopril, its preparation and its use in therapeutics have been described in European patent specification EP 0 049 658.

In view of the pharmaceutical value of this compound, it has been important to be able to obtain it by an effective industrial synthesis process, readily transposable to an industrial scale, that leads to perindopril in a good yield and with excellent purity starting from reasonably priced starting materials.

- 20 Patent specification EP 0 308 341 describes the industrial synthesis of perindopril by the peptide-type coupling of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid benzyl ester with

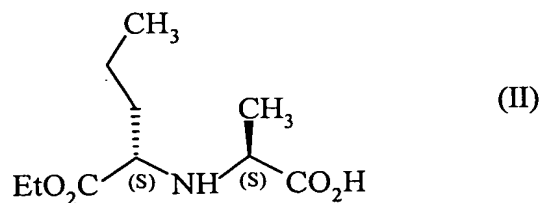
N-[(S)-1-carboxybutyl]-(S)-alanine ethyl ester, followed by deprotection of the carboxylic group of the heterocycle by catalytic hydrogenation.

That process has the advantage of yielding perindopril in a good yield from starting materials for which industrial synthesis has already been described.

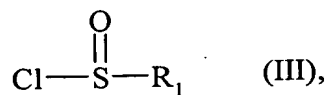
However, it also has drawbacks associated with the use of dicyclohexylcarbodiimide in the coupling step : the formation of coupling impurities, and of dicyclohexylurea, a by-product which is difficult to remove.

The Applicant has now developed a new process for the industrial synthesis of perindopril that avoids the formation of those secondary products.

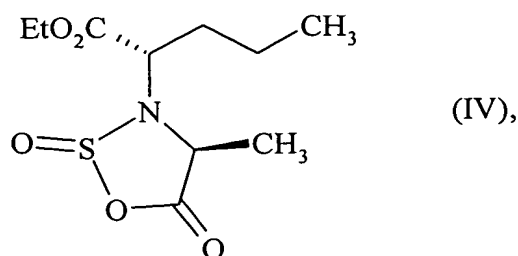
More specifically, the present invention relates to a process for the industrial synthesis of perindopril and its pharmaceutically acceptable salts which is characterised in that the compound of formula (II) :



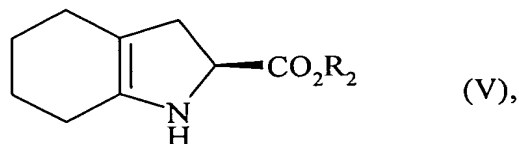
is reacted with a compound of formula (III) :



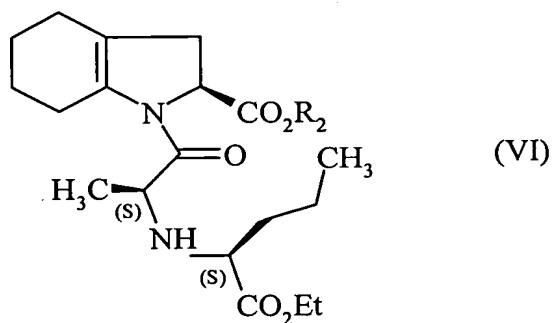
wherein R₁ represents an imidazolyl, benzimidazolyl or tetrazolyl group, to yield the compound of formula (IV) :



which is reacted with a compound of formula (V) :



wherein R₂ represents a hydrogen atom, or a benzyl or linear or branched (C₁-C₆)alkyl group,
 or an addition salt thereof with a mineral or organic acid,
 to yield, after isolation, a compound of formula (VI) :



wherein R₂ is as defined hereinbefore,

which is hydrogenated in the presence of a catalyst such as, for example, palladium, platinum, rhodium or nickel,
 under a hydrogen pressure of from 1 to 30 bars, preferably from 1 to 10 bars, to yield, after deprotection of the acid function where necessary, perindopril of formula (I), which is converted, if desired, into a pharmaceutically acceptable salt, such as the tert-butylamine salt.

The Example hereinbelow illustrates the invention but does not limit it in any way.

EXAMPLE : (2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]-propionyl]octahydro-1H-indole-2-carboxylic acid tert-butylamine salt

Step A : Ethyl (2S)-2-[(4S)-4-methyl-2-oxido-5-oxo-1,2,3-oxathiazolidin-3-yl]-pentanoate

5 Introduce into a reactor 200 g of N-[(S)-ethoxycarbonyl-1-butyl]-(S)-alanine and 1.5 litres of dichloromethane and then, at 0°C, add 325 g of 1H-imidazole-1-sulphonyl chloride. Subsequently, bring the reaction mixture to ambient temperature and then, after stirring for 1 hour, filter off the precipitate formed. The filtrate obtained is evaporated to dryness to yield the expected product in the form of an oil.

10

Step B : (2S)-1-[(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]propionyl]-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylic acid

Introduce 200 g of (2S)-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylic acid and 1.5 litres of dichloromethane into a reactor followed by 180 ml of triethylamine.

15 Subsequently, slowly add a solution of 315 g of the compound obtained in the above Step in 500 ml of dichloromethane and then stir for a further 1 hour at ambient temperature. After the addition of water, the reaction mixture is cooled to 15°C and the pH is adjusted to 4.2 by the addition of a 2N hydrochloric acid solution. Following extraction, the organic phases are washed and then evaporated to yield the expected product.

20 *Step C :* (2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]propionyl]-octahydro-1H-indole-2-carboxylic acid

Introduce into a hydrogenation vessel 200 g of the compound obtained in the above Step in solution in acetic acid, and then 5 g of 10 % Pt/C. Hydrogenate under a pressure of 5 bars at ambient temperature until the theoretical amount of hydrogen has been absorbed.

25 Remove the catalyst by filtration, and then cool to from 0 to 5°C and recover, by means of filtration, the solid obtained. Wash the cake and dry it to constant weight.

Step D : (2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]propionyl}-
octahydro-1H-indole-2-carboxylic acid tert-butylamine salt

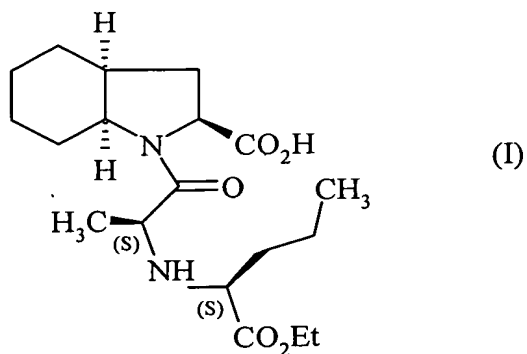
The lyophilisate obtained in the above Step (200 g) is dissolved in 2.8 litres of ethyl acetate, and then 40 g of tert-butylamine and 0.4 litre of ethyl acetate are added.

- 5 The suspension obtained is then refluxed until complete dissolution occurs, and the solution obtained is then filtered in the heated state and cooled, with stirring, to a temperature of from 15 to 20°C.

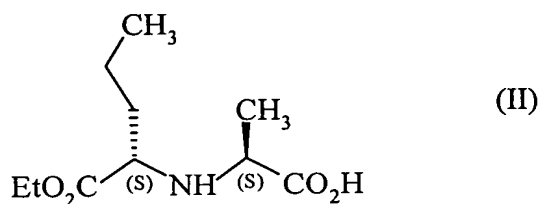
The precipitate obtained is subsequently filtered off, made into a paste again with ethyl acetate, dried and then crushed to yield the expected product in a yield of 95 %.

CLAIMS

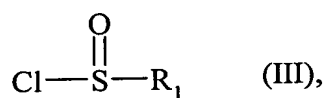
1. Process for the industrial synthesis of the compounds of formula (I) :



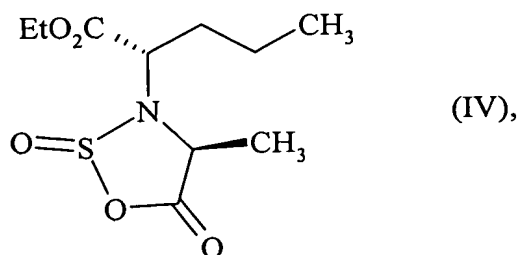
and its pharmaceutically acceptable salts,
characterised in that the compound of formula (II) :



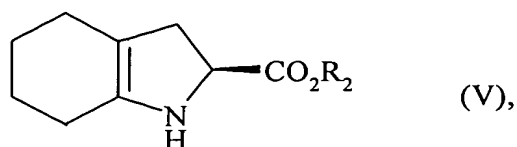
is reacted with a compound of formula (III) :



- 10 wherein R₁ represents an imidazolyl, benzimidazolyl or tetrazolyl group,
to yield the compound of formula (IV) :



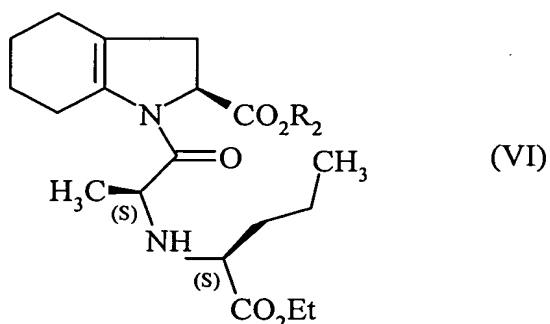
which is reacted with a compound of formula (V) :



wherein R_2 represents a hydrogen atom, or a benzyl or linear or branched (C_1 - C_6)alkyl group,

or an addition salt thereof with a mineral or organic acid,

5 to yield, after isolation, a compound of formula (VI) :



wherein R_2 is as defined hereinbefore,

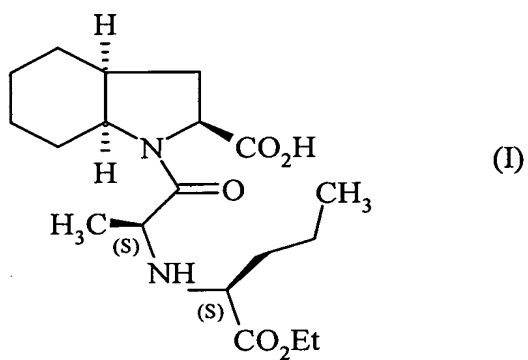
which is hydrogenated in the presence of a catalyst such as, for example, palladium, platinum, rhodium or nickel,

10 under a hydrogen pressure of from 1 to 30 bars, to yield, after deprotection of the acid function where necessary, perindopril of formula (I), which is converted, if desired, into a pharmaceutically acceptable salt, such as the tert-butylamine salt.

2. Synthesis process according to claim 1, characterised in that the hydrogen pressure in the hydrogenation reaction is from 1 to 10 bars.

15 3. Process according to claim 1 for the synthesis of perindopril in the form of its tert-butylamine salt.

Process for the industrial synthesis of perindopril of formula (I) :



5 and its pharmaceutically acceptable salts.